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NITRONES—III[1]

REACTION OF 3,4-DIHYDROISOQUINOLINE N-OXIDE WITH PHOSPHONOYLIDS[2]

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Abstract—Reaction of 3,4-dihydroisoquinoline *N*-oxide **1** with diethyl cyanomethylphosphonate **2** gave the enaminonitrile 1-cyanomethylene-1,2,3,4-tetrahydroisoquinoline **3**. Reaction of **1** with trialkyl phosphonoacetate **4** gave **5**, the fused aziridine derivative 7 - exo - carbethoxy - 1 - aza - 4,5 - benzo - bicyclo[4.1.0]heptene - 4, and the enaminoester 1-carbalkoxymethylene-1,2,3,4-tetrahydroisoquinoline **6**. The ratio of **5**:**6** depends on the reaction conditions. While using 1,2-dimethoxyethane the aziridine **5** is the major product; using alcoholic solvents the yield of **6** increases at the expense of **5** with increasing acidity of the solvent.

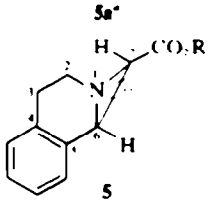
Previously we have shown that the reaction of an acyclic nitrone with triethyl phosphonoacetate leads to aziridines.[3] Subsequently we reported that the reaction of a Δ^1-pyrroline *N*-oxide with phosphonates may be directed to produce either aziridinic or enaminic products.[1,2,4] To extend the scope of this reaction to other systems we have studied the behaviour of 3,4-dihydroisoquinoline *N*-oxide **1** toward some phosphonates. The results of this study are the subject of this paper.

3,4-Dihydroisoquinoline *N*-oxide **1** reacted with diethyl cyanomethyl-phosphonate **2** and sodium hydride in 1,2-dimethoxyethane (DME) at room temperature to one product, identified on the basis of its spectral properties and comparison of these with the literature[6] as 1 - cyanomethylene - 1,2,3,4 - tetrahydroisoquinoline **3**. 3,4-Dihydroisoquinoline *N*-oxide, was also reacted with triethyl phosphonoacetate **4a** and sodium hydride in DME at room temperature. This reaction gave two isomeric products: 7 - exo - carbethoxy - 1 - aza - 4,5 - benzobicyclo[4.1.0]heptene - 4 (**5a**; 57%) and 1 - carbethoxymethylene - 1,2,3,4 - tetrahydroisoquinoline (**6a**; 23%). It was found that products **5** and **6** are not interconvertible under the reaction conditions. The structure of product **6a** was assigned on the basis of the identity of its physical and spectral data with those published.[7]

The structure of compound **5a** was assigned on the basis of its spectral and chemical properties. The NMR spectrum of **5a** exhibits two doublets (J = 2.3 Hz) indicating *trans*-aziridine structure.[8] The assignment of these signals to the two aziridine protons was based on their aromatic solvent induced shifts[9] and was confirmed by preparation and spectral examination of 7-deutero derivative of **5a** using triethyl phosphonoacetate-d_2.

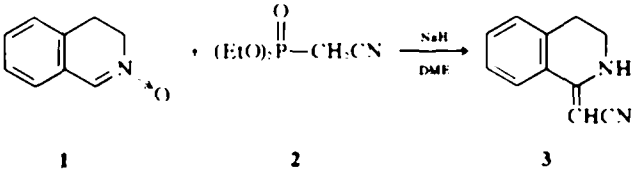
These data are listed in Table 1; passing from chloroform to benzene as solvent, H-6 is shifted

Table 1. Chemical shifts of aziridine protons in **5a** and 7-deutero-**5a***

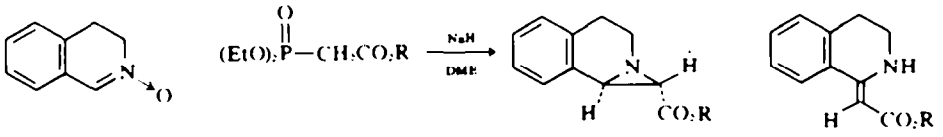


Compound	H-6 δ CDCl₃	H-6 δ C₆D₆	H-7 δ CDCl₃	H-7 δ C₆D₆ ppm
5a	3.40 d*	3.52 d*	2.90 d*	2.73 d*
5a-d	3.33 s	3.40 s	—	—

*For full details of the NMR spectrum of **5a** see Experimental.
*J = 2.3 Hz.



1 **2** **3**



1 **4** **5** **6**

a: R = C_2H_5
b: R = CH_3

downfield, while H-7 is shifted upfield. Since it has been suggested that the molecule of benzene approaches the aziridine from the side away from the lone pair,[9] the more highly shielded proton will be H-7, which is *trans* related to the lone pair. This is confirmed by the spectral results of the deuterated aziridine. Another aspect worthy of pointing out is the fact that in aziridine **5a** as well as in the azabicyclo[3.1.0]hexanes mentioned in our previous paper[1] the aziridine H α to the carbethoxy group appears at the higher field. We have recently suggested[10] that this is a result of a shielding effect exerted by the *cis*-related *N*-alkyl group.

The aziridine structure for **5a** was also confirmed by its cycloaddition with dimethyl acetylenedicarboxylate **7**. It is well documented that properly substituted aziridines readily suffer carbon–carbon bond cleavage to give azomethine-ylides that are capable to enter into cycloaddition with dipolarophiles.[11] Thus, refluxing **5a** with **7** in xylene gave the partially dehydrogenated pyrroloisoquinoline derivative **8** which was further dehydrogenated to the fully aromatic 1,2 - dicarbomethoxy - 3 - carboethoxy - 7,8 - benzo - indolizine **9**. Although the UV spectrum of **9** was found to be identical with that reported for the analogous trimethyl ester,[12] we have synthesized **9** via the corresponding isoquinolinium ylide **10**.[12,13] The two samples of **9** obtained by the two different routes were found to be identical in all respects, thus confirming the aziridine structure for **5a**.

At this point we wish to stress the importance of anhydrous conditions when performing the reaction of nitrone **1** with **4** in DME. In the course of our work we noted that when the solvent used for the reaction was not freshly distilled from lithium aluminum hydride, the yield of enamine **6a** increased of the expense of **5a**. Consequently we consider that the presence of small amounts of water may have decisive importance in the reaction.[14] As a result of these considerations we have decided to examine the reaction between **1** and **4** in protic solvents. We have carried out the reaction of nitrone **1** with phosphonate **4** in methanol (phosphonate **4b**) ethanol **4a** and t-butanol **4a** in the presence of the corresponding sodium alkoxide. The results of these experiments are listed in Table 2. From Table 2 it can be seen that the product ratio changes markedly with the nature of the alcohol as well as with the quantity of the base used.

Previously we have assumed that the reaction between nitrones and phosphonates leads to the formation of an oxazaphospholidine type intermediate.[1,3] Oxazaphospholidine **11** may decompose to the aziridinic product by a concerted mechanism (A). Such fragmentation is presumably initiated by back-donation from the negatively charged exocyclic oxygen. In the presence of protic solvents the negatively charged oxygen in **11** is protonated, resulting in the formation of **12**. This intermediate may undergo a base catalyzed β elimination to yield the enamine (route B). Therefore it can be expected that more acidic solvents, will inhibit formation of the aziridine product by protonation of **11**. This is confirmed by the data in Table 2 showing that in methanol and ethanol, which are both more acidic than t-butanol,[15] the enaminoester is the favoured product, whereas in t-butanol the aziridine predominates. Evidence for the role of the base in the decomposition of **12** to enamine by route (B) is provided by the result from the use of excess base (compare entries 1 and 2 in Table 2).

Table 2. Results from reactions of 3,4-dihydroisoquinoline *N*-oxide with phosphono acetates in alcoholic solvents

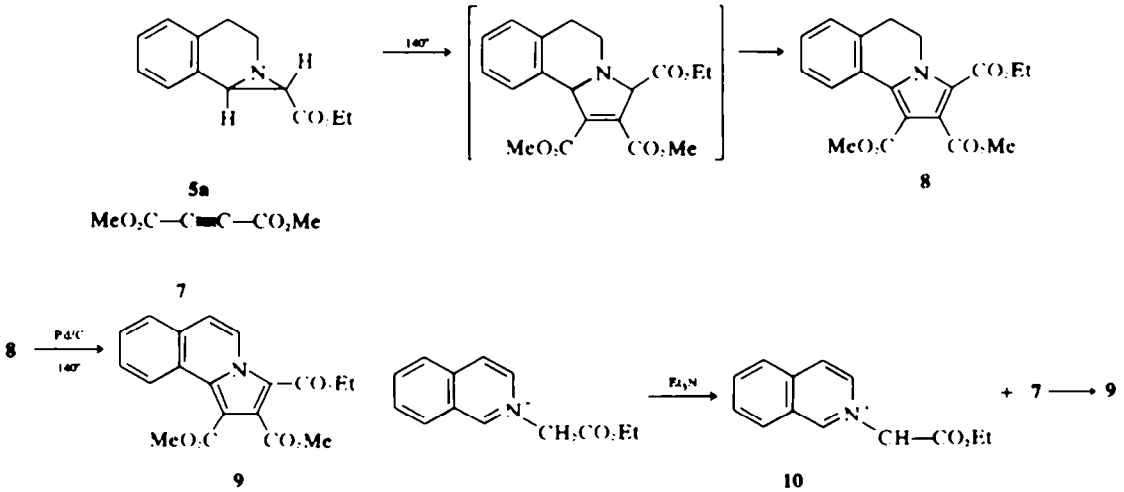
R in ROH and RONA	Equivalents of RONa	% Yield of 5	% Yield of 6
CH_3*	1	14	35
CH_3*	2	3	45
C_2H_5*	1	19	33
$C(CH_3)_3$*	1	22	15

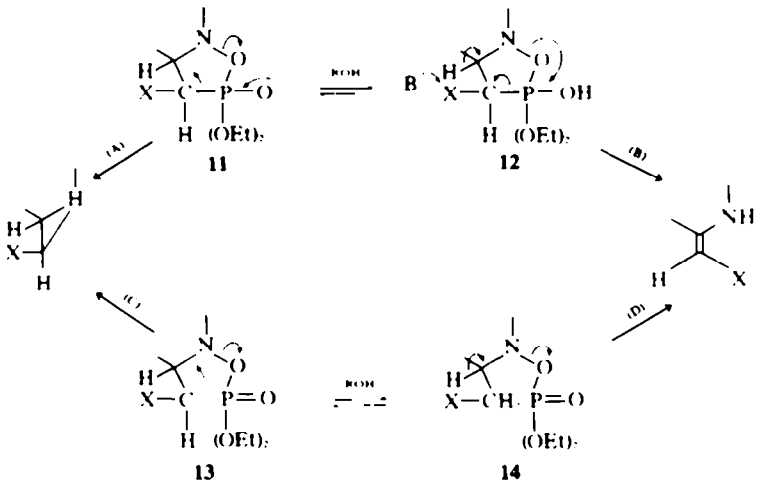
*These reactions were carried out using **4b** and lead to **5b** and **6b**.

*These reactions were carried out using **4a** and lead to **5a** and **6a**.

Alternatively it may be assumed that intermediate **11** undergoes ring-opening to **13**[16] which may decompose to the aziridine by an S_Ni reaction (C) or to the enamine. In recent years the method of perturbation[17] has gained recognition and has been used to treat questions of reactivity and to rationalize some experimental results.[18] This method postulates that the course of reactions of polar species is governed by combinations of two factors, namely charge control and orbital control. For example S_N2 reactions are mainly orbital controlled, while the protonation of a carbanion is mainly charge controlled.[17]

We have noted previously the greater tendency to form enamines from cyanomethylphosphonate than from phosphonoacetate.[1] In this work we also observed that reaction of **2** with **1** gave in all conditions only





enaminonitrile **3**. It has been recognized that an ester function stabilizes an α-negative charge by delocalization, while the cyano group does the same by its inductive effect.[19] Therefore it seems that the difference in the behaviour between phosphonates **2** and **4** may be rationalized on the basis of the perturbation method assuming that intermediate **13** is involved in the reaction. Delocalization of the negative charge in **13** by a carbethoxy group (X = CO_2Et) will decrease the charge control upon its reaction, therefore orbital control will gain a greater relative importance resulting in aziridine formation by an S_Ni reaction (route C).

On the other hand the high charge density on the α-carbon of **13** (X = CN) will increase charge control leading by fast protonation to **14** and to enamine (route D).

The reaction between **1** and **2** was also carried out in ethanol and t-butanol. In both cases only the formation of **3** was observed.

Nitrone **1** did not react with the following phosphonates in NaH-DME: dimethyl methylphosphonate, diethyl phenylthiomethylphosphonate, diethyl α-bromocarbomethoxymethylphosphonate, diethyl α-bromocyanomethylphosphonate.

EXPERIMENTAL[20]

1-Cyanomethylene-1,2,3,4-tetrahydroisoquinoline **3**

0.5 g (10^{-2} mol) 50% dispersion of sodium hydride in mineral oil was washed with petroleum-ether 40–60° (3 × 10 ml) in an inert atmosphere. After evaporation of the residual petroleum-ether, 10 ml of DME (freshly distilled from lithium aluminum hydride) was injected followed by 1.77 g (10^{-2} mol) diethylcyanomethylphosphonate **2** dissolved in 5 ml DME with cooling. After the liberation of hydrogen ceased 1.47 g (10^{-2} mol) 3,4-dihydroisoquinoline *N*-oxide[21] dissolved in 5 ml DME was introduced and the reaction mixture was stirred for 4 h at room temp. DME was evaporated and the residue was taken up in 50 ml ether and 50 ml of water, the ethereal phase was extracted with 30 ml of water and the aqueous phase 3 times with 10 ml ether. The combined ethereal extracts were dried over magnesium sulfate and evaporated, the residue was extracted several times with boiling petroleum-ether (100–120°), yielding 1.5 g (84%) white crystals of **3** m.p. 97–98°, IR (Nujol): 3300, 2175 cm^{-1}; UV (EtOH): 327(1800), 245(3600); NMR ($CDCl_3$): δ 7.65–7.00 4H m, 5.93 1H broad s, 4.31 1H s, 3.57–3.20 2H m, 3.01–2.72 2H m; M.W. Calc. 170. Found (MS) *m/e* = 170, *m/e* = 144(M–CN), *m/e* = 131(M–CHCN); Found: C, 77.64; H, 5.83; N, 16.08. Calc. for $C_{11}H_{10}N_2$: C, 77.64; H, 5.88; N, 16.47%.

General procedure for the reaction of **1** *with* **2** *in alcoholic solvents*

0.23 g (10^{-2} mol) sodium was dissolved in 10 ml of dry alcohol ROH (R = t-Bu, Et) in an inert atmosphere. After the formation of the alkoxide 1.77 g (10^{-2} mol) diethyl cyanomethylphosphonate **2** dissolved in 5 ml of ROH was injected, followed by a solution of 1.47 g (10^{-2} mol) 3,4-dihydroisoquinoline *N*-oxide **1** in 5 ml of ROH. The reaction mixture was stirred for 2 h at 30–40° in the case of t-BuOH and for 2 h at room temp. in the case of EtOH. The excess of the alcohol was removed by vacuum and the residue was extracted with boiling petroleum-ether (100–120°) to give crystalline **3** in yields of 1.25 g (74%) and 1.21 g (71%) in ethanol and t-butanol respectively. These products were found identical in all respects with that obtained in DME with NaH.

Reaction of 3,4-dihydroisoquinoline N-oxide **1** *with triethylphosphonoacetate* **4a**: *formation of* **5a** *and* **6a**

0.5 g (10^{-2} mol) 50% dispersion of sodium hydride in mineral oil was washed with 3 × 10 ml petroleum ether (40–60°) in an inert atmosphere. After evaporation of the residual petroleum ether, 10 ml of DME (freshly distilled from lithium aluminum hydride) was injected, followed by a solution of 2.24 g (10^{-2} mol) triethyl phosphonoacetate **4a** dissolved in 5 ml DME. After the liberation of hydrogen ceased, a solution of 1.47 g (10^{-2} mol) 3,4-dihydroisoquinoline *N*-oxide **1** in 5 ml DME was introduced and the reaction mixture was stirred for 9 hr at room temp. After evaporation of the solvent the residue was taken up in 50 ml ether and 50 ml water, the etheral phase was extracted with 30 ml of water and the water phase with ether (3 × 10 ml).

The combined etheral extracts were dried over magnesium sulfate and concentrated to 5 ml. The white precipitate was removed by decantation and was recrystallized from ethanol to yield 0.75 g of 7 - *exo* - carboethoxy - 1 - aza - 4,5 - benzobicyclo[4.1.0]heptene - 4 **5a** m.p. 115–117°, IR (KBr): 1230, 1750, 3000 cm^{-1}; NMR ($CDCl_3$): δ 7.0–7.6 4H m, 4.2 2H q (J = 7.5 Hz), 3.40 1H d (J = 2.3 Hz), 2.90 1H d (J = 2.3 Hz), 2.8–2.4 4H m, 1.3 3H t (J = 7.5 Hz); (C_6D_6): δ 7.2–6.8 4H m, 4.02 2H q (J = 7.5 Hz), 3.52 1H d (J = 2.3 Hz), 2.73 1H d (J = 2.3 Hz), 2.3–1.9 4H m, 1.15 3H t (J = 7.5 Hz); M.W. Calc. 217. Found (MS) 217; Found: C, 71.74; H, 6.91; N, 6.48. Calc. for $C_{13}H_{15}NO_2$: C, 71.88; H, 6.91; N, 6.45%.

The residue was chromatographed over alumina (activity II; 50 g of alumina for 1 g of the reaction mixture) in chloroform-petroleum ether (40–60°) 3:2. The first fraction contained 0.5 g (23%) 1 - carboethoxymethylene - 1,2,3,4 - tetrahydroisoquinoline **6a**; IR (neat): 1720 cm^{-1}; UV (EtOH): 330(11.400) NMR ($CDCl_3$): δ 8.95 1H broad s, 7.61–7.40 1H m, 7.28–6.85 3H m, 5.01 1H s, 4.02 2H q (J = 6 Hz), 3.41–3.08 2H m, 2.90–2.50 2H m, 1.25 3H q (J = 6 Hz). The second fraction contained 0.475 g of **5a** (total: 57%). The procedure described above was carried out for the synthesis of 7-deutero **3** from triethyl phosphonoacetate-d and *N*-oxide **1**. NMR ($CDCl_3$): δ 3.33 1H s; (C_6D_6): δ 3.40 1H s.

General procedure for the reaction of **1** *with phosphonates* **4a** *and* **4b** *in alcoholic solvents*

0.23 g (10^{-2} mol) sodium was dissolved in 10 ml of the dry alcohol ROH (R = CH_3, Et, t-Bu) in an inert atmosphere, (in the case of R = t-Bu about 9 h of reflux was needed). After the

formation of the alkoxide the phosphonoacetate dissolved in 5 ml of ROH was injected, the reactions in ethanol and t-butanol were run using diethyl carboethoxymethylphosphonate **4a** 2.24 g (10^{-2} mol).

The reactions in methanol were run using diethyl carbomethoxymethylphosphonate **4b** 2, 10 g (10^{-2} mol), followed by a solution of 1.47 g (10^{-2} mol) 3,4-dihydroisoquinoline *N*-oxide **1** in 5 ml of ROH. The reaction mixture was stirred for 18 h at room temp. in the case of CH_3OH and C_2H_5OH, and 9 h at 40° for t-BuOH. The excess of alcohol was removed by vacuum and the residue was separated by thin layer chromatography [alumina G.F. 254, 1 mm, chloroform–petroleum–ether (40–60°) 3:2]. The phosphonoacetate **4a** yielded aziridine **5a** lower band 0.48 g (22%) and 0.42 g (19%) yield in t-butanol and ethanol respectively and enamine **6a** higher band 0.33 g (15%) and 0.70 g (33%) in t-butanol and ethanol respectively by extraction of the adsorbent with boiling chloroform. **5a** and **6a** obtained in these reactions were found to be indentical with products isolated from the reaction of **1** with **4a** in DME.

The reactions in methanol were run using phosphonoacetate **4b**. The products of this reaction were separated by preparative thin layer chromatography (alumina G.F. 254 1 mm, chloroform–petroleum–ether (40–60°) 3:2 and extraction with boiling chloroform. The more polar product was found to be aziridine **5b** 0.29 g (14.2%) oil. NMR ($CDCl_3$): δ 7.35–6.75 5H m, 3.60 3H s, 3.2 1H d (J = 2.3 Hz), 2.80 1H d (J = 2.3 Hz), 2.70–2.31 4H m; MW Calc. 203. Found (MS) 203. The less polar product was the enamine **6b**, oil 0.70 g (34.7%), NMR ($CDCl_3$): δ 9.65 1H broad s; 7.61–7.41 1H m, 7.31–6.90 3H m, 5.07 1H s, 5.09 3H s, 3.48–3.10 2H m, 2.91–2.61 2H m; MW Calc. 203. Found (MS) *m/e* = 203, *m/e* = 172 ($M-OCH_3$), *m/e* = 144 ($M-CO_2CH_3$). The same procedure was carried out using 0.23 g (10^{-2} mol) sodium, 1.05 g (5×10^{-1} mol) diethyl carbomethoxymethylphosphonate **4b** and 0.735 g (5×10^{-1} mol) *N*-oxide **1** in 10 ml CH_3OH to yield 0.038 g (3.5%) **5b** and 0.45 g (43%) **6b**.

1,2 - dicarbomethoxy - 3 - carboethoxy - 5,6 - dihydropyrrolo - [2,1-a]isoquinoline **8**

A solution of 0.05 g (2.5×10^{-1} mol) of **5** and 35 mg dimethyl acetylenedicarboxylate **7** was refluxed in 3 ml xylene in an inert atmosphere for 5 h. Excess xylene was removed by vacuum with the aid of benzene and the residue was separated by a preparative thin layer chromatography (alumina, chloroform–petroleum ether 40–60° 7:3) and recrystallized from ethanol to yield 0.040 g of **8** m.p. 117–119°; IR (Nujol): 1700, 1300, 900 cm^{-1}; UV (EtOH): 300(11600), 248.5(64.000), 240.5(74000), 222(13800): NMR (CCl_4): δ 8.50–8.13 1H m, 7.46–7.10 3H m, 4.58 3H t (J = 6.75 Hz), 4.15 2H q (J = 7.0 Hz), 3.80 6H s, 3.02 2H t (J = 6.75 Hz), 1.35 3H t (J = 7.0 Hz); MW Calc. 357. Found (MS) *m/e* = 357, *m/e* = 326 ($M-OCH_3$), *m/e* = 312 (M–OEt), *m/e* = 285 ($M-CO_2C_2H_5$). Found: C, 63.64; H, 5.64; N, 4.20. Calc. for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.64; N, 3.92%.

1,2-dicarbomethoxy-3-carboethoxy-7,8-benzoindolizidine **9**

A solution of 0.1 g **8**, 0.070 g of palladium on carbon 5% in 2.5 ml xylene was refluxed for 24 h. After filtration and removal of the xylene by the aid of benzene in vacuum, the crude material was recrystallized from ethanol to yield 0.080 g of **9** m.p. 126–128°, IR (Nujol) 2900, 1700, 1250, 750 cm^{-1}, UV (EtOH): 352(11000), 336(9200), 320(7200), 314(7600), 288(19600), 270(120000), 247(17000), 225(13600); NMR (CCl_4): δ 9.50–9.10 2H m, 7.76–7.06 4H m, 4.40 2H q (J = 7 Hz), 3.93 3H s, 3.90 3H s, 1.40 3H t (J = 7 Hz); MW Calc. 355. Found (MS) *m/e* = 355, *m/e* = 324 ($M-OCH_3$), *m/e* = 296 ($M-CO_2CH_3$), *m/e* = 238 ($M-CO_2Et$). Found: C, 64.41; H, 4.89; N, 4.41. Calc. for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.78; N, 3.94%.

N-Carboethoxymethylisoquinolinium bromide

A solution of 2.19 g (0.017 mol) isoquinoline and 3.34 g (0.02 mol) ethyl bromoacetate in 30 ml methylene chloride was warmed for a short period of time on a water bath and the mixture was kept for 2 days in the refrigerator to give 3.24 g white crystals. NMR (D_2O, TSP): δ 8.60–7.83 7H m, 4.80 2H s, 4.43 2H q (J = 7.0 Hz), 1.41 3H t (J = 7.0 Hz); Found: C, 52.59; H, 4.87; N, 4.67; Br, 27.57. Calc. for $C_{13}H_{14}BrNO_2$: C, 52.70; H, 4.72; N, 4.72; Br, 27.02%.

Reaction of N-carboethoxyisoquinolinium bromide with dimethyl acetylenedicarboxylate

This reaction, which was carried out as that described for *N*-carbomethoxyisoquinolinium bromide with dimethyl acetylene dicarboxylate,[12] gave **9**.

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